Report on the Peer Review of the RoC Draft Monograph on Cobalt and Certain Cobalt Compounds

Ruth Lunn, DrPH
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors
December 1–2, 2015
Cobalt Peer-Review Meeting

Outline

- Report on Carcinogens (RoC)
- Cancer hazard evaluation of cobalt
- Peer-review meeting and reports
- NTP conclusions
- Panel comments
- New gentoxicity studies
- Next steps
The Report on Carcinogens (RoC) is congressionally mandated

- Public Health Service Act, Section 301(b)(4) (1978, amended 1993)
  - Directs Secretary, Health and Human Services (HHS) to publish a list of carcinogens
  - Lists substances as “known” or “reasonably anticipated human carcinogens”
- Identifies substances that pose a cancer hazard for people in the United States
- NTP prepares the RoC for the Secretary, HHS
- Each edition of the report is cumulative

http://ntp.niehs.nih.gov/go/roc
NTP process for preparing the RoC

Current status in cobalt review

**Nomination and Selection of Candidate Substances**
- Invite nominations to the RoC
  - Interagency review
  - Public comment
- Develop draft concept documents for substances proposed for evaluation
  - Public comment
- Review of draft concept documents by NTP Board of Scientific Counselors*
  (public meeting, public comment)
  - NTP Director
- Select candidate substances

**Scientific Evaluation of Candidate Substances**
- Prepare draft RoC Monograph for a candidate substance
  (initiate cancer evaluation component)
  - External scientific input, as needed
    (e.g., consultants, ad hoc presentations, expert panels*)
  - Public input
    (e.g., listening session, comment)
  - Interagency input
    (complete cancer evaluation component and prepare draft substance profile)
  - Interagency review
- Complete draft RoC Monograph

**Public Release and Peer Review of Draft RoC Monographs**
- Release draft RoC Monograph
  - Public comment
  - Peer review of draft RoC Monograph by NTP Peer-Review Panel*
    (public meeting, public comment, peer-review report)
  - Present information regarding the peer review and revised draft RoC Monograph to NTP Board of Scientific Counselors*
    (public meeting, public comment)
  - NTP Director
- Finalize RoC Monograph
  (cancer evaluation component and substance profile)

**HHS Approval and Release of Latest Edition of the RoC**
- Submit recommended listing status for newly reviewed candidate substances
  - NTP Executive Committee
- Approval of listing status by Secretary, HHS
  (transmit latest edition of RoC to Congress and release to the public)

**Key**
- HHS = Health and Human Services
- NTP = National Toxicology Program
- RoC = Report on Carcinogens
* Federally chartered advisory groups
Defining the candidate substance

From cobalt metal to a class of cobalt forms

Cobalt is a naturally occurring metallic element that exists in different forms

- Cobalt compounds exist in different valence states, and as inorganic or organic forms
- Varying water solubility and bioaccessibility

Cobalt metal
- Cobalt metal nominated based on NTP bioassay

Cobalt
- Expanded scope in concept document to “cobalt”

Cobalt and certain cobalt compounds*
- Based on input from informational group

*Release cobalt ion *in vivo*

In the absence of *in vivo* or *in vitro* assays, bioaccessibility can be predicted by solubility in artificial biological fluids.

Class does not include Vitamin B12, which does not release ions *in vivo*
Cobalt and cobalt compounds

Significant exposure to cobalt from both occupational and non-occupational sources

Metallurgical uses (> 62%)
- Superalloys and other alloys
- Medical such as joint implants

Chemical uses (27%)
- Pigments, driers, catalysts, adhesives
- Animal diets

Cemented carbides and bonded diamonds (9%)
- Tungsten carbides (“hard metals”)
- Steel with microdiamonds impregnated into surface cobalt layer

Electronics and green energy (< 1%)
- Rechargeable batteries (computers, mobile phones, vehicles)
Time was set aside at the peer-review meeting to discuss scientific issues raised in the public comments.
## Cobalt peer-review panel

<table>
<thead>
<tr>
<th>Member</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>Melissa A. McDiarmid, MD, MPH, DABT</td>
<td>University of Maryland School of Medicine</td>
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<tr>
<td>(Chair)</td>
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<tr>
<td>Lisa De Roo, MPH, PhD</td>
<td>University of Bergen</td>
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<tr>
<td>Robert F. Herrick, SD</td>
<td>Harvard School of Public Health</td>
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<tr>
<td>C. William Jameson, PhD</td>
<td>CWJ Consulting, LLC</td>
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<tr>
<td>John LaPres, PhD</td>
<td>Michigan State University</td>
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<tr>
<td>Clark Lantz, PhD</td>
<td>The University of Arizona</td>
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<tr>
<td>Marie-Elise Parent, PhD</td>
<td>Université du Québec</td>
</tr>
<tr>
<td>Michael V. Pino, DVM, PhD, DACVP</td>
<td>Consultant, Veterinary Toxicological Pathology and Preclinical Drug Development</td>
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<tr>
<td>John Pierce Wise, Sr., PhD</td>
<td>University of Louisville</td>
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<tr>
<td>Anatoly Zhitkovich, PhD</td>
<td>Brown University</td>
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NTP BSC liaison: George B. Corcoran
<table>
<thead>
<tr>
<th>Charge</th>
<th>Actions (votes)</th>
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</thead>
<tbody>
<tr>
<td>To comment on the draft cancer evaluation component, specifically,</td>
<td>Whether the scientific evidence supports the NTP’s preliminary listing decision for cobalt and certain cobalt</td>
</tr>
<tr>
<td>whether it is technically correct and clearly stated, whether the</td>
<td>compounds in the RoC</td>
</tr>
<tr>
<td>NTP has objectively presented and assessed the scientific evidence,</td>
<td>Whether the scientific evidence supports the NTP’s conclusions on the level of evidence for carcinogenicity from</td>
</tr>
<tr>
<td>and whether the scientific evidence is adequate for applying the</td>
<td>cancer studies in humans and experimental animals of cobalt and certain cobalt compounds</td>
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<tr>
<td>listing criteria</td>
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<tr>
<td>To comment on the draft substance profile, specifically, whether</td>
<td></td>
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<tr>
<td>the scientific justification presented in the substance profile</td>
<td></td>
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<tr>
<td>supports the NTP’s preliminary policy decision on the RoC listing</td>
<td></td>
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<tr>
<td>status of cobalt and certain cobalt compounds</td>
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Post peer-review steps

Monograph revised based on Panel comments

Peer-review report
- Recommendations on NTP draft conclusions
- Scientific and technical peer-review comments

Revised draft monograph
- Revised based on NTP review of peer-review comments

NTP response to the peer-review report
- Responses to comments
- Rationale for accepting/not accepting peer-review recommendations
The Panel agreed with draft NTP conclusions

<table>
<thead>
<tr>
<th>Evidence stream</th>
<th>NTP draft recommendation</th>
<th>Panel</th>
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<tbody>
<tr>
<td>Human cancer studies</td>
<td>Data are inadequate to evaluate the relationship between exposure to cobalt and cancer</td>
<td>Agreed</td>
</tr>
<tr>
<td>Cancer studies in experimental animals</td>
<td>Sufficient evidence</td>
<td>Agreed</td>
</tr>
<tr>
<td>Mechanistic data</td>
<td>Mechanisms of carcinogenicity of cobalt and cobalt compounds involves cobalt ion</td>
<td>Agreed</td>
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</table>

Listing recommendation

Reasonably anticipated to be a human carcinogen*

*Recommended that definition of certain compounds, release cobalt ion in vivo, be part of the listing
Rationale for grouping as a class

Cobalt ion is proposed to be key in pathways of carcinogenicity

- **Cobalt Form**
  - Soluble Cobalt Compounds
  - Poorly Soluble Cobalt Particles

- **Cellular Uptake**
  - Ion channels
  - Endocytosis (lysosomal dissolution)

- **Intracellular \( \text{Co}^{2+} \)**
  - Genotoxicity
  - DNA repair inhibition
  - ROS/oxidative stress
  - HIF-1\( \alpha \) stabilization

- **Modes of Actions**
  - Genomic stability
  - Oxidative damage
  - Hypoxia-responsive target genes
  - Resistance to apoptosis

- **Early Key Events**
  - Accumulation of critical mutations
  - Dysregulation of cell growth and proliferation

- **Late Key Events**
  - Tumor Development
**Rationale for listing cobalt as a class**

Cobalt metal and compounds cause similar biological effects associated with carcinogenicity

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Soluble cobalt salts</th>
<th>Cobalt metal</th>
<th>Poorly soluble cobalt compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CoCl₂</td>
<td>CoSO₄</td>
<td>Particles</td>
</tr>
<tr>
<td>Bioaccessibility</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lysosome*</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gastric</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cellular uptake</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>ROS</td>
<td>+</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>HIF-1α stabilization</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>DNA repair inhibition</td>
<td>+</td>
<td>ND</td>
<td>+</td>
</tr>
<tr>
<td>Genotoxicity * in vitro</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Genotoxicity * in vivo</td>
<td>+</td>
<td>ND</td>
<td>–</td>
</tr>
</tbody>
</table>

ND = no data

* Dissolution of cobalt particles in lysosomal fluid is a key component for the proposed mechanisms
Similar carcinogenic effects

Sufficient evidence of carcinogenicity from studies in experimental animals

<table>
<thead>
<tr>
<th>Animal Neoplasms</th>
<th>Soluble cobalt salts</th>
<th>Cobalt metal*</th>
<th>Poorly soluble cobalt compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CoCl$_2$</td>
<td>CoSO$_4$</td>
<td>particles</td>
</tr>
<tr>
<td>Lung</td>
<td>ND</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>ND</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Injection site</td>
<td>+</td>
<td>ND</td>
<td>+</td>
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* Cobalt metal
  - Pancreatic islet tumors (exposure related)
  - Mononuclear cell leukemia (exposure related)
  - Kidney tumors (equivocal)

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Panel’s comments on the draft monograph

Scientific and technical comments to improve the quality of the monograph or other conclusions

• Cobalt clastogenic but not mutagenic

• No scientific disagreements with NTP major conclusions
  – Specific comments addressed in the response document

• Cobalt-containing joint implants (vote)
  – Recommended NTP review the literature on human cancer studies
  – Convene another peer review if relevant data that might change the evaluation were identified
Joint implant studies are not informative for evaluating effects of cobalt *per se*

- Studies identified by literature search
  - 30 case reports that specifically mentioned a tumor (malignant fibrous histiocytoma, sarcoma, NHL) at site of cobalt-containing implant; rare occurrence
  - 16 cohort studies and 1 patient series

- Limitations of studies for evaluating cobalt
  - Study design (e.g., case reports)
  - Lack of specificity (other types of implants or metals)
  - Limited sensitivity and inadequate information on extent of cobalt exposure
  - Underlying comorbidities
Cobalt Development Institute (CDI) sponsored genotoxicity studies

• Shared a recently accepted publication of genotoxicity studies (Kirkland *et al.* 2015)
  – NTP and the panel did not review the data at the meeting because of inadequate time, given the size (over 100 pages) and proximity to the meeting (2 days)
  – CDI presented an overview of the findings at the meeting

• Project consisted of over 40 genotoxicity studies
  – Provided genotoxicity information for “new” compounds, i.e., not reported on in the peer-review literature (10/16 tested substances)
  – Provided information on mutagenicity for new and previously tested compounds
New studies unlikely to change NTP conclusions

- Findings of the individual studies are largely consistent with NTP conclusions concerning specific genotoxic endpoints
  - Mostly negative mutagenicity findings in bacteria and mammalian cells
  - Clastogenic in other *in vitro* studies
  - Unclear findings in *in vivo* studies
- Little impact on rationale for listing cobalt compounds as a class or biological plausibility of the mechanisms of carcinogenicity
- Discussed in NTP response to the peer-review report but not in revised monograph
Next Steps

Process for preparation of the RoC

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Acknowledgements

Office of the RoC
  Gloria Jahnke
  Diane Spencer (co-project leader)

Contractor Staff
  Sanford Garner (PI)
  Stanley Atwood (co-project leader)
  Susan Dakin (editorial assistance)
  Ella Darden
  Andrew Ewens
  Jessica Geter
  Alton Peters
  Tracy Saunders
  Pam Schwingl

Peer-Review Panel

Technical Advisors and Information Group Members
  Mamta Behl, PhD, DABT (Information Group Moderator)
  Chad Blystone, PhD, DABT
  Janet Carter, MPH (OSHA/DOL)
  Michelle Hooth, PhD, DABT
  Arun Pandiri, PhD, DACVP
  Matthew Stout, PhD, DABT
  Erik Tokar, PhD
  John Wheeler, PhD, DABT (ATSDR/CDC)

Office of Liaison, Policy and Review
  Mary Wolfe
  Lori White

NIEHS and Interagency Scientists:
  Internal Review
Questions